Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendments. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**". No new matter has been added. Reconsideration of the pending claims is respectfully requested.

Amendments to the claims

Claims 1, 3, 5, 6 and 8 are amended to overcome the rejection of claims under 35 U.S.C. §112, first paragraph. Claims 2, 4, 7, 9 and 10 are canceled. No new matter has been added.

The 35 U.S.C. §112, first paragraph rejection

Claims 1-10 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully traversed.

The rejection of claims 2, 4, 7, 9 and 10 is moot, because these claims are cancelled.

The Examiner states that the methods of increasing or decreasing the expression of p21 recited in the instant claims are not clearly defined, and therefore encompass gene therapy and antisense therapy. According to the Examiner, there is a high degree of unpredictability in the fields of gene therapy, antisense therapy, and suppression of organ transplants. Such unpredictability in the relevant art is considered together with the breadth of the claims, the lack of working examples and guidance in the specification, and the high degree of skill required. These factors amount to a requirement of undue experimentation in order to perform the broadly claimed method.

The Applicant respectfully disagrees with the Examiner's assertions. According to the Examiner, the state of the art at the time of filing considers the success of gene and antisense therapy to be unpredictable, as discussed by **Crystal** (*Science* 270: 404-410, 1995), **Verma** *et al.* (*Nature* 389: 239-242 (1997), **Walther and Stein** (*Drugs* 60: 249-271 (2000), and **Branch** (*TIBS* 23: 45-50 (1998). Major difficulties discussed include the design of delivery systems and vector construction so as to provide sufficient levels of gene expression after delivery. The difficulties involved in gene

therapy notwithstanding. Applicant contends that there has been ample groundwork laid in the field of gene therapy to guide one skilled in the art in practicing the invention of the claims, as amended, with a reasonable expectation of success. **Anderson** (*Nature* 392: 25-30, 1998) states that as of February 1998, over 300 clinical protocols involving gene therapy had been approved in the US (page 29). **Anderson** also predicts that the next 5 years of research should produce statistically significant clinical data showing that gene-therapy protocols can improve the condition of patients, and that clinical trials of vectors that can target specific tissues should have begun (page 30). In fact, there have already been several cases where gene therapy has been successful to treat diseases such as severe combined immunodeficiency disease and sickle cell anemia (**Culver** *et al.*, *Transplantation Proceedings* 23: 170-171, 1991; **Hoogerbrugge** *et al.*, *Human Gene Therapy* 3: 553-558, 1992; **Siegel-Itzkovich**, *BMJ* 325: 10, 2002; **Bertrand**, *J. Nat. Med. Assoc. 94: A9-A10, 2002*). **Branch** also acknowledges advances in the field of antisense therapy: "Today's peak specificity, whatever it is, will almost certainly rise as current strategies are optimized and advances in nucleic acid chemistry bring derivatives with fewer side effects" (page 47).

Additionally, the Applicant points out that the claims as amended, which cite the reduction or elimination of *p21* gene expression, are sufficiently supported by the specification to enable one skilled in the art to practice the invention without undue experimentation. The specification discloses gene therapy, antisense therapy, and genetic manipulation as some of the possible ways to accomplish such a reduction or elimination of *p21* gene expression (page 9, lines 8-10), and discloses experiments employing partial renal ablation as a model of chronic renal failure from diverse causes (page 10, lines 9-11). Mice expressing a homozygous null mutation in *p21* are clearly demonstrated to be highly resistant to the deleterious effects of partial renal ablation. The experimental results disclosed indicate that *p21* has a critical role in the functional and morphological consequences subsequent to the stress of renal ablation, including the development of glomerular sclerosis and hypertension, and that these symptoms may be critically linked to the prominent role of *p21* in regulating the cell cycle (page 29, lines 4-15). Removal of *p21* expression allowed the growth response after partial renal ablation to be relatively more hyperplastic, so that the kidney work load is then better accommodated (page 30, lines 1-3).

The striking effects seen in the *in vivo* experiments disclosed allow a reasonable prediction that reducing or eliminating *p21* gene expression will be able to ameliorate or prevent the effects of acute renal stress or chronic renal failure.

Finally, the Applicant points out that the prior art has of yet brought about no causal link between early glomerular hypertrophy and hyperfunction, and later hypertension, and the progressive nature of renal disease (page 2, lines 11-20 and page 3, lines 1-5). The present application provides such a link in clearly demonstrating that controlling *p21* expression can prevent progressive renal disease *in vivo*. The known methods in the art may therefore be used by skilled practitioners to practice the present claims in targeting *p21* expression, thereby improving upon the current methods of treating or preventing long-term renal failure.

The Applicant therefore contends that the level of development and skill in the art is sufficient to allow the practice of the present claims as amended, and accordingly respectfully requests

that the rejection of claims 1-10 under 35 U.S.C. 112, first paragraph, be withdrawn.

This is intended to be a complete response to the Office Action mailed August 15, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: Oct 21, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend claim 1 to read as follows:

1. (amended) A method for treating or preventing a pathophysiological state of ~~an organ~~ a kidney in an individual, wherein said state is characterized by an undesirable level of cyclin-dependent kinase inhibitor activity in said ~~organ~~ kidney, comprising the step of ~~regulating~~ reducing or eliminating the expression of the *p21* gene in said ~~organ~~ kidney of said individual.

Please amend claim 3 to read as follows:

3. (amended) The method of claim 1, wherein said pathophysiological state is selected form the group consisting of renal fibrosis, glomerulosclerosis, reduced filtration rates, and hypertension, ~~and organ transplantation rejection~~.

Please amend claim 5 to read as follows:

5. (amended) The method of claim ~~4~~ 1, wherein the reduction or elimination of the expression of the *p21* gene is

performed by a technique selected from the group consisting of drug therapy, and genetic manipulation.

Please amend claim 6 to read as follows:

6. (amended) A method for treating or preventing chronic progressive renal failure in an individual, comprising the step of ~~regulating~~ reducing or eliminating the expression of the *p21* gene in one or both kidneys of said individual, wherein said ~~regulation~~ reducing or eliminating the expression of the *p21* gene results in the manipulation of cyclin-dependent kinase inhibitor activity in one or both kidneys.

Please amend claim 8 to read as follows:

8. (amended) The method of claim ~~7~~ 6, wherein the reduction or elimination of the expression of the *p21* gene is performed by a technique selected from the group consisting of drug therapy, and genetic manipulation.

Please cancel claims 2, 4, 7, 9 and 10.